Management and treatment of osteonecrosis in children and adolescents with acute lymphoblastic leukemia

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ABSTRACT

There is no consensus regarding how to manage osteonecrosis in pediatric acute lymphoblastic leukemia patients. Therefore, we performed a quality assessment of the literature with the result of a search strategy using the MESH terms osteonecrosis, children, childhood cancer, surgery, bisphosphonates, 6 hydroxymethyl-glutaryl CoA reductase inhibitors, anticoagulants and hyperbaric oxygen, and terms related to these MESH terms. A randomized controlled trial showed that osteonecrosis can be prevented by intermittent, instead of continuous, corticosteroid administration. The studies on interventions after onset of osteonecrosis were of low-quality evidence. Seven pediatric acute lymphoblastic leukemia studies described non-surgical interventions; bisphosphonates (n=5), hyperbaric oxygen therapy (n=1), or prostacyclin analogs (n=1). Safety and efficacy studies are lacking. Five studies focused on surgical interventions; none was of sufficient quality to draw definite conclusions. In conclusion, preventing osteonecrosis is feasible in a proportion of the pediatric acute lymphoblastic leukemia patients by discontinuous, instead of continuous, steroid scheduling. The questions as to how to treat childhood acute lymphoblastic leukemia patients with osteonecrosis cannot be answered as good-quality studies are lacking.

Introduction

Osteonecrosis is one of the complications that can occur during pediatric acute lymphoblastic leukemia (ALL) treatment.[1] The sequelae of osteonecrosis belong to the most severe long-term complications of treatment for pediatric ALL.[2-4] The severity of osteonecrosis may range from asymptomatic to debilitating, causing severe pain, reduction in joint mobility and, finally, degenerative changes. The general presumed pathological mechanism is a compromised blood circulation of the bone, leading to cell death. During revascularization, bone resorption by osteoclasts results in demineralization and trabecular thinning, and subsequently mechanical failure.

Osteonecrosis appears to have a multifactorial origin. Glucocorticoid therapy has been identified as the main contributing factor to osteonecrosis in childhood ALL patients.[5] Other agents may also contribute to the development of osteonecrosis. Previously, we found that a hypercoagulable state due to the interaction of corticosteroids and asparaginase may contribute to an impaired circulation and subsequently lead to osteonecrosis.[6] In addition, it is hypothesized that the folate-antagonist methotrexate may cause homocysteinemia which can lead to venous vascular occlusion.[7]

The risk of osteonecrosis is age-dependent, with adolescents being more prone to develop osteonecrosis than both young children and adults.[8,9] As an increasing number of younger adults receive pediatric ALL treatment protocols rather than adult protocols,[10] with the concomitant higher steroid doses, the incidence of osteonecrosis in this adolescent population may increase further. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI) provide a severity scale for osteonecrosis with 1 being asymptomatic osteonecrosis diagnosed by radiological screening, and stage 2 to 4 indicating symptomatic osteonecrosis gradually increasing from mild to disabling symptoms.[11] Treatment of osteonecrosis primarily aims to prevent progression of osteonecrosis, prevent collapse, and obtain pain relief and improvement of joint mobility. In clinical practice, management of osteonecrosis depends on the stage and symptoms of osteonecrosis, the phase of treatment, and patient specific characteristics like age and lifestyle. There is no consensus on how osteonecrosis needs to be managed in pediatric ALL patients.

We performed a narrative review, to describe which antileukemic therapy adjustments have been considered, to prevent osteonecrosis in children and adolescents treated for ALL. In addition, we carried out a quality assessment of the literature on treatment options of osteonecrosis in ALL patients. Our goal is to give an overview of the treatment options for osteonecrosis in pediatric ALL patients and to elucidate the effectiveness of these treatment options to reduce symptoms and prevent progression. Finally, we attempt to compose a tool for clinical decision making regarding the prevention and management of osteonecrosis in pediatric ALL patients based on the best available evidence.

Methods

Search strategy

The databases used for this review were PubMed/Medline and The Cochrane Central Register of Controlled Trials (CENTRAL). To identify studies to be included or considered for this review, a detailed

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search strategy was developed (*Online Supplementary Table S1*) with the following MESH terms as main subjects: osteonecrosis, children, childhood cancer, surgery, bisphosphonates, 6 hydroxymethyl-glutaryl CoA reductase inhibitors, anticoagulants and hyperbaric oxygen. We placed no restrictions on the type of study, so randomized controlled trials (RCTs), as well as non-randomized studies (NRS), case series and single case reports were reviewed. To identify additional eligible articles, we screened the reference lists of the retrieved reviews. Moreover, those reviews specifically focusing on the influence of corticosteroid dosing and timing to prevent osteonecrosis in pediatric ALL were used to describe which antileukemic therapy adjustments could be considered. Only English language articles that had been published since 1990 until 1st August 2013 were included. Finally, we searched for existing guidelines for treatment of osteonecrosis in the Clinical Practice Guidelines (National Guideline Clearinghouse (NGC)) and The Cochrane Collaboration.

Types of participants and diagnostic criteria

With this study, we aimed to find evidence for a guideline to prevent osteonecrosis and to intervene at time of occurrence of osteonecrosis in patients with ALL aged 0 to 21 years. As we acknowledge the small number of studies that address the population of interest, all studies on preventive and therapeutic strategies for osteonecrosis that partially address the population of interest (part of the study population >21 years or no inclusion of ALL patients only) were reviewed in order to support decision making.

We did not make any restrictions on which joints were affected. Articles on osteonecrosis of the jaw (which is defined as "presence of exposed bone in the oral cavity which does not heal within eight weeks" and which is another entity to the osteonecrosis described here) were excluded. The diagnosis of osteonecrosis had to be confirmed with radiological data (e.g. X-ray, computed tomography (CT), magnetic resonance imaging (MRI), Tc99 bone scan). Studies that do not describe the criteria used to establish the diagnosis of osteonecrosis were excluded.

Types of interventions

As there is as yet no consensus on which types of interventions are preferably used to treat symptomatic osteonecrosis in pediatric ALL patients, we included studies that describe the outcome of surgical as well as non-surgical management of osteonecrosis. Any length of treatment and, for drug therapy, all administration routes were considered.

Types of outcome measures and adverse events

For the studies on prevention of osteonecrosis, we used incidence rates of osteonecrosis as outcome parameter. The primary outcomes for the intervention studies were recovering of osteonecrosis lesions indicated by improvement of the clinical grade of the lesions, or alternatively the delay in progression of osteonecrosis measured by radiological imaging techniques. The clinical grade of lesions may be expressed as NCI criteria,[11] and/or the Harris hip score[12] or the d'Aubigné and Postel score,[13] all addressing pain relief, improvement of joint mobility, and improvement of joint function. Radiological outcome may be measured by imaging techniques such as X-ray, CT or MRI, and comprises reduction of the involved surface area or volume, reduction of the number of localizations, improvement of sclerotic changes and bone fragmentation, improvement of formed sequesters, or improvement of radiological staging (e.g. Ficat and Arlet[14] or the Association of Research Circulation Osseous (ARCO)[15]). Secondary outcomes were defined as reduction of the use of analgesics, improvement of the quality of life, and the need for subsequent surgery. Follow-up time was defined as: short (≤2 years after intervention), intermediate (2-5 years after intervention), and long (≥5 years after intervention). We summarized the effects of the interventions on outcome parameters by classifying them as positive, stable or worsened outcome.

Adverse events were defined as any effect not listed as an outcome and reported as a side effect by the authors or judged as such by us. The events were classified as: immediate (less than 24 h after intervention); early (1-8 days after intervention); and long term (>8 days after intervention).

Study selection, quality assessment and presentation

After employing the search strategy described above, the initial screening on title and abstract of identified references was performed by one reviewer. Possibly relevant articles were purchased as full text articles and a final selection was made based on the aforementioned inclusion criteria. Additionally, a screening on methodological quality was performed by a checklist that had been designed before starting the review (*Online Supplementary Appendix)*. This methodological appraisal was performed by one reviewer (MLW). A random sample of 25% of the full-text articles was reviewed by a second reviewer (EDW) to evaluate agreement between reviewers (κ statistic). Moreover, in case of doubt about eligibility by the first reviewer, articles were reviewed by the second reviewer. Discrepancies between the 2 reviewers were resolved by the consultation of a third independent reviewer (MMHE). To assess the quality of the included studies, we categorized them into 5 levels of evidence based on study design and number of included patients (*Online Supplementary Table S2A and B*). Results are presented in a descriptive way, and were evaluated by the other reviewers (the authors).

Results

Results of the search strategy

Running the searches in the electronic database of PubMed/Medline yielded a total of 4412 English language references published after 1990 (after exclusion of duplicates). *Online Supplementary Figure S1* illustrates a flowchart of study identification and selection. Initial screening from the title and/ or abstract excluded 4228 references, based on discussing osteonecrosis of the jaw (n=70) or not being within the scope of the review/not describing an intervention (n=4158). The remaining 184 articles were fully assessed. A total of 104 articles were excluded after assessing the full-text article. Thirty articles were reviews and were, therefore, used for cross referencing which did not result in any further inclusions. Seven articles on preventive strategies to reduce the development of osteonecrosis in children or adolescents with ALL were extracted from the 30 reviews. A search of the Cochrane Central Register of Controlled Trials (CENTRAL) and the Clinical Practice Guidelines (NGC) did not identify additional articles or guidelines about the treatment of osteonecrosis in children and adolescents. Fourteen articles specifically described pediatric ALL patients[16-29] and 36 articles partially addressed the population of interest.[30-65] Of those 14 articles specifically describing pediatric ALL patients, 7 reported the results of non-surgical interventions and 7 reported the results of surgical interventions for osteonecrosis.

Quality assessment

The reviewers were in excellent agreement on articles for inclusion, with a κ statistic of 0.9. *Online Supplementary*

Table S3 shows an overview of the quality assessment of the preventive strategies, as well as the non-surgical and surgical interventions. The 7 studies on preventive strategies that were extracted from the 16 reviews, showed consistent results and most were of high quality (level 1). Of the 14 included pediatric ALL intervention studies, the majority had a level of evidence of 4-5 (n=12); there was one study with a level of evidence of 3, and one with a level of evidence of 2. No randomized controlled trials on intervention for osteonecrosis met the inclusion criteria of the current study. Therefore, we can only give recommendations on interventional approaches that are supported with low to moderate evidence from literature.

Preventive strategies: antileukemic therapy adjustments

Seven of the 16 reviews addressed the influence of the administration schedule of corticosteroids (cumulative dose, type of corticosteroid, continuous *vs.* discontinuous administration) on the incidence of osteonecrosis in pediatric ALL as preventive strategy.[1,3,66-70] Dexamethasone is not indisputably more toxic to the skeleton than prednisone.[67] The DFCI investigators retrospectively compared dexamethasone and prednisone as post-remission corticosteroid between 2 consecutive studies in ALL patients aged 0-18 years and they found no difference in the 5-year cumulative incidence of osteonecrosis.[4] Nonetheless, a later study of the same group randomized between prednisone and dexamethasone in the post-induction phase and reported a higher 5-year cumulative incidence of osteonecrosis for those receiving dexamethasone when aged 10 years or over.[71] Similarly, the COG study group only found a difference in incidence of osteonecrosis when using dexamethasone compared to prednisone during induction phase for patients aged 10 years or over.[72,73] On the other hand, the UK Medical Research Council (patients aged 1-18 years), the BFM-group (patients aged 1-17 years), and the Tokyo Children's Cancer Study Group (patients aged <10 years) found no difference in the incidence of osteonecrosis between patients receiving prednisone and dexamethasone.[74-76] Finally, we prospectively investigated the cumulative incidence of symptomatic osteonecrosis in pediatric ALL patients aged 1-18 years using a treatment protocol with a relatively high cumulative dose of dexamethasone (1244-1370 mg/m^2) and found an incidence of 6%, which is not higher than incidences reported by other studies using lower doses.[9] Dose reduction of corticosteroids might be beneficial, as data from multiple ALL trials show a higher incidence of osteonecrosis with higher cumulative doses of corticosteroids.[77,78] However, both the use of multi-agent treatment protocols, and the use of different conversion rates for dexamethasone to prednisone make it difficult to compare data of various protocols. In an MRI-screening study, dexamethasone plasma levels turned out to be higher in those with grade 3-4 osteonecrosis than in those with lower grade osteonecrosis or those without osteonecrosis, even after adjusting for age.[79]

However, ALL cells from older ALL patients tend to be more resistant to corticosteroids than ALL cells from young children,[80,81] making it questionable to recommend lower doses of corticosteroids to offset the lower clearance observed in older patients with ALL. Interestingly, timing of dexamethasone may be more relevant than the cumulative dose, because osteonecrosis occurs less frequently with intermittent administration of corticosteroids than with continuous corticosteroid schedules.[82] This positive effect of a 'steroid holiday' was first shown in a mouse model.[83] Recently a randomized clinical trial, including ALL patients aged 10 years or over, confirmed that the dosing schedule of corticosteroids during post-induction intensification supersedes the effect of the cumulative exposure of corticosteroids on the development of treatment-related osteonecrosis.[84,85]

Glucocorticoids are directly toxic to osteocytes, inducing apoptosis and resulting in osteonecrosis. Glucocorticoid exposure also leads to lipid infiltration of the marrow and osteocyte hypertrophy, causing increased intramedullary pressure and consequent reduced blood-flow. Epiphyseal closure during puberty may reinforce this process. Intermittent corticosteroid administration probably allows for recovery of this intramedullary pressure. The exact pathophysiology for the lower osteonecrosis rates with this intermittent administration of corticosteroids is still unknown. In addition, in the randomized trial of Mattano *et al.*, we cannot rule out the possibility that the difference in osteonecrosis rates between the two arms may be due to other differences in the chemotherapy schedule.

When considering adjustments of corticosteroid schedules, the risk of impairment of the event-free survival (EFS) of ALL always needs to be taken into consideration. Mattano *et al.* described a trend toward improved EFS among osteonecrosis patients and speculated that this could be due to the high corticosteroid sensitivity in osteonecrosis patients.[2] In our recently published prospective study of the Dutch Childhood Oncology Group (DCOG), we could not find a higher EFS in patients with osteonecrosis.[9]

In conclusion, prevention of treatment-related osteonecrosis is feasible by discontinuous, instead of continuous, steroid scheduling in patients at high risk of osteonecrosis. Although it remains difficult to adequately define patients at high risk for osteonecrosis, at least older age and female gender are risk factors. As osteonecrosis has been reported in pediatric cancer patients who did not receive corticosteroids,[33,86] also other antileukemic therapy adjustments might be considered in the future, such as asparaginase and methotrexate that may interact with glucocorticoids.[6,83] Yet, there is not enough evidence in the literature to support advising adjustments such as limiting asparaginase or methotrexate dose. Finally, genetic variation may determine susceptibility to drug toxicity and influence the risk profile of osteonecrosis in ALL.

Non-surgical interventions for osteonecrosis in pediatric ALL patients

Seven studies focused on non-surgical interventions for osteonecrosis in pediatric ALL patients (*Online Supplementary Table S4A*). Five studies provided data on bisphosphonates,[17,19,23,26,27] one study described an intervention with hyperbaric oxygen therapy,[20] and one study reported on a prostacyclin analog.[24] No studies compared the effectiveness of different antileukemic therapy adjustments as treatment option after the onset of osteonecrosis on the symptoms or radiological progression of osteonecrosis. *Online Supplementary Table S5* shows the reported outcomes for the different non-surgical interventions. The five articles on bisphosphonates (alendronate, pamidronate and zoledronate) in small numbers of pediatric ALL patients describe some positive effect on pain

and range of motion, but no favorable effect on the radiological outcome.[17,19,23,26,27] As no proper controls were used in these studies, the real benefit for these drugs was not shown. Side effects consisted of acute phase reactions (headache, fever, nausea, vomiting, malaise), mainly after the first infusion.

The study on hyperbaric oxygen therapy in pediatric patients with ALL (n=21) / non-Hodgkin lymphoma (n=6) included not only patients with osteonecrosis but also those with bone marrow edema.[20] Of the 27 patients, only 19 gave informed consent for hyperbaric oxygen therapy; the other 8 patients were considered as controls. This way of allocating patients to an intervention or a control group leads to the risk of selection bias. All patients became pain-free, and there was no difference in the need for surgery between patients with and without hyperbaric oxygen therapy. Only mild adverse events occurred, such as eardrum irritation and middle ear irritation.

The study on the prostacyclin analog (iloprost) in 7 patients with pediatric ALL and one with Hodgkin lymphoma did not have controls, so no conclusions can be drawn from this study.[24] In addition, part of the patients underwent core decompression prior to the iloprost treatment, which may substantially affect the outcomes. The reported side-effects were headache, nausea, vomiting and phlebitis.

Surgical interventions for osteonecrosis in pediatric ALL patients

Seven studies described surgical interventions for osteonecrosis in pediatric ALL patients (*Online Supplementary Table S4B*), including bone or cartilage stimulating methods, containment-improving or pressure relieving methods and joint replacements. Three case series of, in total, only 7 pediatric ALL patients described the implantation of autologous osteogenic cells.[16,18,22] As these 3 studies used no controls, no conclusions can be drawn on the efficacy of these methods. Osteochondral grafting suggested a favorable outcome in 5 of the 6 patients, but again without proper controls.[21,28] One study described resurfacing arthroplasty in 14 young patients with hematologic malignancies.[25] In this exploratory study, younger age and larger osteonecrosis lesions were significant risk factors for failure. One case report described an exceptional hip reconstruction procedure with a subtrochanteric valgus extension osteotomy and distal femoral lengthening using an external fixator.[29]

Discussion

As there is no evidence-based consensus on how osteonecrosis needs to be managed in pediatric ALL patients, we reviewed the possible preventive strategies for osteonecrosis in this patient population. We reviewed the current status of valid antileukemic therapy adjustments to prevent osteonecrosis. Regarding the interpretation of these data, one should keep in mind the many differences in scheduling between therapy protocols. Moreover, the use of multiple agents simultaneously makes it difficult to distinguish the effect of corticosteroids from other antileukemic agents. Lastly, different studies use various equivalent dose calculations to compare prednisone and dexamethasone doses. The generally assumed equivalent dose ratio of prednisone *versus* dexamethasone is 7; however, we feel that there is evidence from literature that this ratio may be substantially higher.[87] Therefore, higher osteonecrosis rates and better survival rates with dexamethasone compared to prednisone, that are sometimes reported based on studies using a ratio of less than 7, may not be reliable. There is evidence that reducing the cumulative dose of corticosteroids may reduce the osteonecrosis rate; however, the risk of impairment of the event-free survival (EFS) of ALL needs to be considered carefully. Moreover, reducing the risk of treatment-related osteonecrosis is feasible by discontinuous, instead of continuous, steroid administration in a subset of patients with ALL at increased risk of osteonecrosis. Although, it remains difficult to adequately define those high-risk patients, at least older age and female gender are risk factors for osteonecrosis.[9] When considering chemotherapy adjustments after the onset of osteonecrosis, the possible negative effects on the event-free survival (EFS) of ALL need to be carefully discussed. Despite the fact that there are some studies suggesting that both asparaginase and methotrexate contribute to the development of osteonecrosis, there is still not enough evidence in the literature to advise adjustments of these agents.

In addition, we reviewed possible treatment options for osteonecrosis in pediatric ALL patients. The majority of these studies were of low-quality evidence, so there is insufficient evidence to confidently judge all treatment options. A significant problem in determining the effectiveness of interventions for osteonecrosis was that most studies lacked proper control populations. Moreover, in studies that did describe a control population, there was often selection bias as patients were frequently assigned to an intervention based on the stage of osteonecrosis or risk factors for deterioration or collapse. Interventions for osteonecrosis were performed in different phases of chemotherapeutic treatment or after cessation of treatment, which hampers the comparison of outcomes. Furthermore, most included studies only had a short follow up (<5 years).

Non-surgical interventions for osteonecrosis that were reported in children and adolescents with ALL were administration of bisphosphonates, hyperbaric oxygen therapy and a prostacyclin analog. As these studies all included low numbers of patients and most did not use control populations, there is no evidence for the benefits of these interventions in practice. Currently, there are no safety and efficacy studies available to support the use of these agents in children treated for ALL. As the risk for osteonecrosis of the jaw was reported in adult patients receiving bisphosphonates, it may be interesting to note that this side-effect was never reported in children. Within osteonecrosis lesions, bisphosphonates are active in the revascularized bone. The majority of the bisphosphonates, however, are active in the remainder of the skeleton, resulting in a systemic effect of bisphosphonates.[88] This systemic effect might be of benefit in pediatric ALL patients with osteonecrosis, as often multiple joints are involved and because of the additional (unintentional) positive effects on bone density; but there is no evidence of this. As hypercoagulability and hyperlipidemia have been associated with osteonecrosis in animal studies and *in vitro* studies, one could suppose that administration of anticoagulants or lipid-lowering agents might be beneficial. However, studies on the administration of low-molecular weight heparin or statins were not performed in pediatric ALL patients or in other pediatric populations or

in adult patients with ALL.

An extensive review of the effect of orthopedic techniques is beyond the scope of this article. To interpret data of surgical interventions, it is important to acknowledge that not only changes in biomechanics are influencing the outcome, but also an increased blood flow and an altered activity pattern. Moreover, interpretation of data is complicated by the fact that reported surgical interventions were performed in different stages of osteonecrosis and either directly or after failure of non-surgical approaches. When there is already severe deterioration or collapse, surgical treatment may be inevitable. This review, however, shows that only low-quality studies on surgical interventions were available in children and adolescents with ALL, so we cannot reliably advise in favor of the effectiveness of surgical interventions. Joint replacements in a young patient may not be preferable as the long life expectancy and their active lifestyle give an increased risk of multiple revisions, with subsequent negative effects on quality of life.[25,89] Moreover, it should always be taken into consideration that the symptoms of osteonecrosis are reversible in a large proportion of the patients.[9]

Clinical decision making on the management of osteonecrosis in pediatric ALL

Although we realize that evidence-based clinical decision making regarding the management of osteonecrosis in pediatric ALL patients based on the available literature is not possible, recommendations can be given based on expert opinion. To develop a clinical practice guideline, future high-quality research on efficacy and safety of interventions for osteonecrosis in childhood ALL is necessary.

Prevention of osteonecrosis is more relevant than cure, and the risk of treatment-related osteonecrosis can be reduced by discontinuous, instead of continuous, steroid administration. When antileukemic therapy adjustments are considered, this always has to be balanced against the primary goal of cure of ALL.

We propose clinical screening of osteonecrosis, focused on persistent pain in arms or legs independent of vincristine administration, limping and/or limited range of motion of joints. This seems to be more relevant than radiological screening in ALL patients, as there is no clear evidence that in cases of asymptomatic osteonecrosis any intervention might prevent progression to symptomatic osteonecrosis. Moreover, many asymptomatic osteonecrosis patients do not go on to experience symptomatic disease at all.[79] We advise clinical screening for symptomatic osteonecrosis until three years after diagnosis, as the large majority (>90%) of the patients in our recently published prospective study developed symptoms of osteonecrosis during therapy.[9] In addition, Strauss *et al*. reported that the cumulative incidence of osteonecrosis showed a relatively fast increase during the first three years after diagnosis of ALL and reached a plateau phase afterwards.[4] Similarly, Mattano *et al*. found in the CCG-1882 only 1 out of 111 patients and in the CCG-1961 only 4 out of 143 patients with symptomatic osteonecrosis beyond three years after diagnosis of ALL.[2,84] Special awareness of symptomatic osteonecrosis is recommended in patients at high risk of osteonecrosis. Risk factors for osteonecrosis are age 10 years or over, female gender and the use of a high dose of corticosteroids, as these factors are consistently found to contribute to the development of osteonecrosis.[2,9] In case of symptoms, MRI is the preferable method to diagnose osteonecrosis.[90]

Despite clear evidence, weight-bearing restrictions and adequate pain management are advised in patients with osteonecrosis based on biological plausibility. In case of osteonecrosis diagnosed on MRI, lesion size (i.e. surface area of a joint or lesion volume) seems to be the best predictor for clinical joint outcome.[91,92] Lesions occupying more than 30% of the joint surface show high likelihood of joint deterioration or collapse, and, therefore, non-surgical treatment options may be considered. As no safety and efficacy studies on these non-surgical treatment options, such as bisphosphonates, are available, these agents need to be taken forward as part of a clinical trial. Surgical interventions during or shortly after ALL treatment are discouraged, because of the self-limiting course of osteonecrosis in the majority of the pediatric ALL patients.[9,93] Only in case of severe deterioration or collapse of a joint may surgical treatment be required, and joint preserving methods are preferred to partial or total joint replacements.

Conclusion

Preventing treatment-related osteonecrosis is feasible in a subset of patients with ALL at increased risk of osteonecrosis by discontinuous, instead of continuous, steroid scheduling. Although an extensive search was performed to answer the question as to how to treat childhood cancer patients with osteonecrosis, the question cannot be answered as there are no good quality studies. To develop a clinical practice guideline, future high-quality research on efficacy and safety of interventions for osteonecrosis in childhood ALL is necessary.

Authorship and Disclosures

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